Amendments to the Specification:

Please replace the paragraph beginning at line 12, page 7 with the following replacement paragraph:

Preferred optical dyes include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade Blue™, and Texas Red. Suitable optical dyes are described in the Sixth Edition of the Molecular Probes Handbook by Richard P. Haugland, hereby expressly incorporated by reference in its entirety; see chapters 1, 2 and 3 in particular. Many fluorophores are commercially available as derivatives that will react with amines (chapter 1), thiols (chapter 2) and other functional groups including alcohols, aldehydes, ketones, carboxylic acids, etc (chapter 3). Also preferred are fluorescent lanthanide metal ion chelates, including, but not limited to, ~~Er~~ Eu, Tb, and Dy, as are known in the art.

Please replace the paragraph beginning at line 15, page 3 with the following replacement paragraph:

Accordingly, the present invention provides methods for making modified nucleosides comprising a covalently attached signalling moiety or signalling moiety precursor. By "nucleoside" herein is meant a base attached to a ribose (furan). The base may be any base that can form an anhydro-structure, as defined below, including naturally ~~occuring~~ occurring and non-naturally ~~occuring~~ occurring bases. Suitable bases include, but are not limited to, uracil, thymine, cytosine and inosine, and base analogs such as ~~xathanine~~ xanthine, ~~hypoxathanine~~ hypoxanthine, isocytosine, halogenated bases such as 5-halo-uracil (e.g. 5-bromo- or 5-iodo-uracil), etc. The ribose may be either ribose or ribose analogs such as the five membered carbon ring analogs, etc. Accordingly, as used herein, the term "nucleoside" includes nucleoside analogs. While the nucleic acids of the present invention will generally contain phosphodiester bonds, in some cases nucleic acid analogs are included that may have alternate backbones, comprising, for example, phosphoramide (Beaucage et al., Tetrahedron 49(10):1925 (1993) and references therein; Letsinger, J. Org. Chem. 35:3800 (1970); Sprinzl et al., Eur. J. Biochem. 81:579 (1977); Letsinger et al., Nucl. Acids Res. 14:3487 (1986); Sawai et al, Chem. Lett. 805 (1984), Letsinger et al., J. Am. Chem. Soc. 110:4470 (1988); and Pauwels et al., Chemica Scripta 26:141 91986)), phosphorothioate (Mag et al., Nucleic Acids Res. 19:1437 (1991); and U.S. Patent No. 5,644,048), phosphorodithioate (Briu et al., J. Am. Chem. Soc. 111:2321 (1989), O-~~methylphophoroamidite~~ methylphosphoramidite linkages (see Eckstein, Oligonucleotides and Analogues: A Practical Approach, Oxford University Press), and peptide nucleic acid backbones and linkages (see Egholm, J. Am. Chem. Soc. 114:1895 (1992); Meier et al., Chem. Int. Ed. Engl. 31:1008 (1992); Nielsen, Nature, 365:566 (1993); Carlsson et al., Nature 380:207 (1996), all of which are incorporated by reference). Other analog nucleic acids include those with positive backbones (Denpcy et al., Proc. Natl. Acad. Sci. USA 92:6097 (1995); non-ionic backbones (U.S. Patent Nos. 5,386,023, 5,637,684, 5,602,240, 5,216,141 and 4,469,863; Kiedrowshi et al., Angew. Chem. Intl. Ed. English 30:423 (1991); Letsinger et al., J. Am. Chem. Soc. 110:4470 (1988); Letsinger et al., Nucleoside & Nucleotide 13:1597 (1994); Chapters 2 and 3, ASC Symposium Series 580, "Carbohydrate Modifications in Antisense Research", Ed. Y.S. Sanghui and P. Dan Cook; Mesmaeker et al., Bioorganic & Medicinal Chem. Lett. 4:395 (1994); Jeffs et al., J. Biomolecular NMR 34:17 (1994); Tetrahedron Lett. 37:743 (1996)) and non-ribose

backbones, including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, "Carbohydrate Modifications in Antisense Research", Ed. Y.S. Sanghui and P. Dan Cook. Nucleic acids containing one or more carbocyclic sugars are also included within the definition of nucleic acids (see Jenkins et al., Chem. Soc. Rev. (1995) pp169-176). Several nucleic acid analogs are described in Rawls, C & E News June 2, 1997 page 35. All of these references are hereby expressly incorporated by reference. These modifications of the ribose-phosphate backbone may be done for a number of reasons, including for example to increase the stability and half-life of such molecules in physiological environments.

Please replace the paragraph beginning at line 7, page 5 with the following replacement paragraph:

As will be appreciated by those in the art, all of these nucleic acid analogs may find use in the present invention. In addition, mixtures of naturally occurring nucleic acids and analogs can be made; for example, at the site of signalling moiety attachment, an analog structure may be used. Alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally ~~occuring~~ occurring nucleic acids and analogs may be made.

Please replace the paragraph beginning at line 12, page 5 with the following replacement paragraph:

As used herein, the term "nucleosides" may also include nucleotides, i.e. nucleosides with phosphate groups attached, and nucleotide analogs as outlined above. Thus, for example, having synthesized a modified nucleoside, a triphosphate nucleotide may be formed, or a phosphoramidite form of the nucleoside may be formed, for incorporation into a nucleic acid. "Nucleic acid" in this context means two or more nucleosides joined together, and can have any combination of natural and synthetic bases, including uracil, adenine, thymine, cytosine, guanine, inosine, ~~xanthanine~~ xanthine, ~~hypoxanthanine~~ hypoxanthine, isocytosine, isoguanine, halogenated bases, etc.

Please replace the paragraph beginning at line 19, page 5 with the following replacement paragraph:

By "modified nucleoside" herein is meant a nucleoside comprising a signalling moiety or signalling moiety precursor (i.e. a polydentate ligand) covalently attached to the 2' or 3' position of the ribose (or the equivalent position in a ribose analog). By "signalling moiety" herein is meant any moiety which can be used to detect the nucleoside or nucleic acid into which it is incorporated. As will be appreciated by those in the art, the characterization and identity of the signalling moiety will depend on the desired detection method. Thus, for example, signalling moieties comprising electron transfer moieties, optical dyes including fluorochromes and chromophores, chemiluminescent and electrochemiluminescent labels, magnetic resonance imaging (MRI) agents, enzymes, haptens and other binding ligands to which a labelled binding partner may be attached (e.g. ~~digeoxigenin~~ digoxigenin, biotin, antigens, nucleic acids, etc.), can all be attached to nucleosides using the methods of the present invention, as long as a derivative can be made that includes a primary amine that does not eliminate its signalling properties.

Please replace the paragraph beginning at line 1, page 8 with the following replacement paragraph:

In a preferred embodiment, the electron transfer moieties are transition metal complexes. Transition metals are those whose atoms have a partial or complete d shell of electrons. Suitable transition metals for use in the invention include, but are not limited to, cadmium (Cd), copper (Cu), cobalt (Co), palladium (Pd), zinc (Zn), iron (Fe), ruthenium (Ru), rhodium (Rh), osmium (Os), rhenium (Re), ~~platinium~~ platinum (Pt), scandium (Sc), titanium (Ti), Vanadium (V), chromium (Cr), manganese (Mn), nickel (Ni), Molybdenum (Mo), technetium (Tc), tungsten (W), and iridium (Ir). That is, the first series of transition metals, the platinum metals (Ru, Rh, Pd, Os, Ir and Pt), along with Fe, Re, W, Mo and Tc, are preferred. Particularly preferred are ruthenium, rhenium, osmium, ~~platinium~~ platinum, cobalt and iron.

Please replace the paragraph beginning at line 20, page 9 with the following replacement paragraph:

In a preferred embodiment, organometallic ligands are used. In addition to purely organic compounds for use as redox moieties, and various transition metal coordination complexes with δ-bonded organic ligand with donor atoms as heterocyclic or exocyclic substituents, there is available a wide variety of transition metal organometallic compounds with π-bonded organic ligands (see Advanced Inorganic Chemistry, 5th Ed., Cotton & Wilkinson, John Wiley & Sons, 1988, chapter 26; Organometallics, A Concise Introduction, Elschenbroich et al., 2nd Ed., 1992, VCH; and Comprehensive Organometallic Chemistry II, A Review of the Literature 1982-1994, Abel et al. Ed., Vol. 7, chapters 7, 8, 10 & 11, Pergamon Press, hereby expressly incorporated by reference). Such organometallic ligands include cyclic aromatic compounds such as the cyclopentadienide ion [C5H5(-1)] and various ring substituted and ring fused derivatives, such as the indenylide (-1) ion, that yield a class of ~~bis(cyclopentadieyl)metal~~ bis(cyclopentadienyl) metal compounds, (i.e. the metallocenes); see for example Robins et al., J. Am. Chem. Soc. 104:1882-1893 (1982); and Gassman et al., J. Am. Chem. Soc. 108:4228-4229 (1986), incorporated by reference. Of these, ferrocene ~~[(C5H5)2Fe]~~ [$(C_5H_5)_2Fe$] and its derivatives are prototypical examples which have been used in a wide variety of chemical (Connelly et al., Chem. Rev. 96:877-910 (1996), incorporated by reference) and electrochemical (Geiger et al., Advances in Organometallic Chemistry 23:1-93; and Geiger et al., Advances in Organometallic Chemistry 24:87, incorporated by reference) electron transfer or "redox" reactions. Metallocene derivatives of a variety of the first, second and third row transition metals are potential candidates as redox moieties that are covalently attached to either the ribose ring or the nucleoside base of nucleic acid. Other potentially suitable organometallic ligands include cyclic arenes such as benzene, to yield bis(arene)metal compounds and their ring substituted and ring fused derivatives, of which bis(benzene)chromium is a prototypical example, Other acyclic π-bonded ligands such as the allyl(-1) ion, or butadiene yield potentially suitable organometallic compounds, and all such ligands, in ~~conjuction~~ conjunction with other π-bonded and δ-bonded ligands constitute the general class of organometallic compounds in which there is a metal to carbon bond. Electrochemical studies of various dimers and oligomers of such compounds with bridging organic ligands, and additional non-bridging ligands, as well as with and without metal-metal bonds are potential candidate redox moieties in nucleic acid analysis.

Please replace the paragraph beginning at line 10, page 11 with the following replacement paragraph:

In addition to transition metal complexes, other organic electron donors and acceptors may be covalently attached to the nucleoside using the methods of the invention. These organic molecules include, but are not limited to, riboflavin, xanthene dyes, azine dyes, acridine orange, *N,N'*-dimethyl-2,7-diazapyrenium dichloride (DAP^{2+}), methylviologen, ethidium bromide, quinones such as N,N'-dimethylanthra(2,1,9-*def*:6,5,10-*d'e'f'*)diisoquinoline dichloride ($ADIQ^{2+}$); porphyrins ([meso-tetrakis(N-methyl-x-pyridinium)porphyrin tetrachloride], varlamine blue B hydrochloride, Bindschedler's green; 2,6-dichloroindophenol, 2,6-dibromophenolindophenol; Brilliant crest blue (3-amino-9-dimethyl-amino-10-methylphenoxyazine chloride), methylene blue; Nile blue A (aminoaphthodiethylamino phenoxazine sulfate), indigo-5,5',7,7'-tetrasulfonic acid, indigo-5,5',7-trisulfonic acid; phenosafranine, indigo-5-monosulfonic acid; safranine T; bis(dimethylglyoximato)-iron(II) chloride; induline scarlet, neutral red, anthracene, coronene, pyrene, 9-phenylanthracene, rubrene, binaphthyl, DPA, phenothiazene, fluoranthene, phenanthrene, chrysene, 1,8-diphenyl-1,3,5,7-octatetracene, naphthalene, acenaphthalene, perylene, TMPD and analogs and ~~subsitituted~~ substituted derivatives of these compounds.

Please replace the paragraph beginning at line 4, page 22 with the following replacement paragraph:

When a metal ion complex is a component of the signalling moiety, synthesis may occur in several ways. In a preferred embodiment, the ligand(s) are added to a nucleoside, followed by the metal ion, and then the nucleoside with the metal ion complex attached is added to an oligonucleotide, i.e. by addition to the nucleic acid synthesizer. Alternatively, the ligand(s) may be attached, followed by ~~incorportation~~ incorporation into a growing oligonucleotide chain, followed by the addition of the metal ion.

Please replace the paragraph beginning at line 12, page 23 with the following replacement paragraph:

If required, the target sequence is prepared using known techniques. For example, the sample may be treated to lyse the cells, using known lysis buffers, electroporation, etc., with purification and/or amplification such as PCR ~~occuring~~ occurring as needed, as will be appreciated by those in the art.

Please replace the paragraph beginning at line 8, page 24 with the following replacement paragraph:

A variety of hybridization conditions may be used in the present invention, including high, moderate and low stringency conditions; see for example Maniatis et al., Molecular Cloning: A Laboratory Manual, 2d Edition, 1989, and Short Protocols in Molecular Biology, ed. Ausubel, et al, hereby incorporated by ~~referencee~~ reference. The hybridization conditions may also vary

when a non-ionic backbone, i.e. PNA is used, as is known in the art. In addition, cross-linking agents may be added after target binding to cross-link, i.e. covalently attach, the two strands of the hybridization complex.

Please replace the paragraph beginning at line 19, page 25 with the following replacement paragraph:

In a preferred ~~emboidment~~ embodiment, PCR primers are made comprising signalling moieties, and detection of target sequences utilizes the incorporation of the labelled PCR products.

Please replace the paragraph beginning at line 14, page 26 with the following replacement paragraph:

~~Syntheis~~ Synthesis of polydentate nucleoside

Please replace the paragraph beginning at line 15, page 26 with the following replacement paragraph:

This example is directed to the synthesis shown in Figure 2. 2-amino-ethylpyridine may be ~~subsituted~~ substituted as well.

Please replace the paragraph beginning at line 13, page 27 with the following replacement paragraph:

To uridine that was slurried in dimethylformamide (DMF) was added diphenylcarbonate and heated to 110/C for 8 hours (step **a**). The product, 2,2'-O-anhydro-1-(β-D-arabinofuranosyl) uracil, was purified by flash column chromatography. The cyclized intermediate, 2,2'-O-anhydro-1-(β-D-arabinofuranosyl) uracil, was dissolved in dichloromethane (CH_3Cl_2) and a catalytic amount of dimethylaminopyridine (DMAP) added along with a 1.1 excess of dimethoxytrityl chloride (DMTCl) and kept at room temperature for 24 hours (step **b**). The solution was evaporated to dryness and purified by flash column chromatography. The purified product, 5'-O-(4,4'-Dimethoxytrityl)-2,2'-O-anhydro-1-(β-D-arabinofuranosyl) uracil, was dissolved in CH_3Cl_2 and 2 equivalents of 1,1'-carbonyldiimidazole added and allowed to react for 24 hrs (step **c**). To this solution was added 1 equiv of diisopropylethylamine (DIEA) and 1.1 equiv. of 2-aminomethylpyridine and allowed to react for and additional 24 hours (step **d**). After purification (not necessary) the intermediate product formed from step **d** was suspended in tetrahydrofuran (THF) and 1,8-diazabicyclo-undec-7-ene (DBU) added and allowed to react for 48 hours (step **e**). The resulting material, 5'-O-(4,4'-dimethoxytrityl)-2'-N,3'-O-(2-oxooxazolidinyl)-2'-aminomethylpyridyl-2'-deoxyruidine, was treated with NaOH in methanol/water for 24 hours at room temperature (step **f**). The resulting product, 5'-O-(4,4'-dimethoxytrityl)-2'-iminomethylpyridyl-2'-deoxyuridine, was dissolved in ethanol and $Ru(acac)_2(CH_3CN)_2$ (impy) was added to the solution (step **g**); where acac = acetylacetonate and

impy = 5'-O-(4,4'-dimethoxytrityl)-2'-iminomrthylpyridyl-2'-deoxyuridine). The reaction was refluxed for 4 hr under argon, filtered, the solvent removed under reduced pressure, and the residue purified by flash chromatograph to yield bis(acetylacetonate)ruthenium(II)-5'-O-(4,4'-dimethoxytrityl)-2'-iminomethylpyridyl-2'-deoxyuridine. To bis(acetylacetonate)ruthenium(II)-5'-O-(4,4'-dimethoxytrityl)-2'-iminomethylpyridyl-2'-deoxyuridine and (dimethylamino)pyridine was added succinic anhydride. The reaction was stirred for 19 hr. at room temperature under positive pressure argon. The solvent was removed and the residue co-evaporated with toluene. The residue was purified by flash chromatography and a saturated aqueous solution of ammonium ~~hexaflurophosphate~~ hexafluorophosphate was added to the precipitate the product, bis(acetylacetonate)ruthenium(II)-5'-O-(4,4'-dimethoxytrityl)-2'-iminomethylpyridyl-2'-deoxyuridine phosphoramidite (step 𝕙).